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## (54) THERAPEUTIC AGENT FOR ANGINA PECTORIS

## (57) Abstract:

PURPOSE: To obtain a therapeutic agent for angina pectoris, stable as a medicine due to its heat resistance, solubility in water and stability in aqueous solutions, hardly causing toxicity and side effects, having antimicrobial activities and without requiring the use of a preservative in formulation.

CONSTITUTION: This safe therapeutic agent for angina pectoris contains a peptide, obtained by hydrolyzing lactoferrin of mammals, apolactoferrin and/or the lactoferrin saturated with a metal with an acid or an enzyme and having any of specific 31 amino acid sequences, a pharmaceutically permissible derivative of the peptide, pharmaceutically permissible salts of the peptide or a mixture of two or more thereof as an active ingredient. The resultant therapeutic agent has persistent remitting actions on fit of the angina pectoris and slight side effects. Sequences expressed by formulas I to IX (R01 is an optional amino acid residue except Cys), etc., are cited as the amino acid sequence of the peptide. The therapeutic agent is parenterally administered in a dose of  $\cdot 10$   $\mu$ g per kg body weight and orally administered in a dose of  $\cdot 10$ mg per kg body weight.

THE PEPTIDE SEQUENCE OF THE THERAPEUTIC AGENT FOR ANGINA PECTORIS IS AS FOLLOWS:  
 FORMULA I:  $\text{H}_2\text{N}-\text{R}_1-\text{NH}_2$  (R1: 31 AMINO ACID SEQUENCE)  
 FORMULA II:  $\text{H}_2\text{N}-\text{R}_2-\text{NH}_2$  (R2: 31 AMINO ACID SEQUENCE)  
 FORMULA III:  $\text{H}_2\text{N}-\text{R}_3-\text{NH}_2$  (R3: 31 AMINO ACID SEQUENCE)  
 FORMULA IV:  $\text{H}_2\text{N}-\text{R}_4-\text{NH}_2$  (R4: 31 AMINO ACID SEQUENCE)  
 FORMULA V:  $\text{H}_2\text{N}-\text{R}_5-\text{NH}_2$  (R5: 31 AMINO ACID SEQUENCE)  
 FORMULA VI:  $\text{H}_2\text{N}-\text{R}_6-\text{NH}_2$  (R6: 31 AMINO ACID SEQUENCE)  
 FORMULA VII:  $\text{H}_2\text{N}-\text{R}_7-\text{NH}_2$  (R7: 31 AMINO ACID SEQUENCE)  
 FORMULA VIII:  $\text{H}_2\text{N}-\text{R}_8-\text{NH}_2$  (R8: 31 AMINO ACID SEQUENCE)  
 FORMULA IX:  $\text{H}_2\text{N}-\text{R}_9-\text{NH}_2$  (R9: 31 AMINO ACID SEQUENCE)

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**CLAIMS**

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[Claim(s)]

[Claim 1] The anginal drug which makes an active principle the derivative of the peptide which has the amino acid sequence of a publication in either of the array number 1 to the array numbers 31, and these peptides permitted pharmacologically, the salts of these peptides permitted pharmacologically, or two or more sorts of such mixture.

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[Translation done.]

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DETAILED DESCRIPTION

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[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to an anginal drug. This invention makes an active principle the peptide of the lactoferrin origin which has a specific amino acid sequence etc. in more detail, and it is related with a new anginal drug without a side effect.

[0002]

[Description of the Prior Art] Since angina is a syndrome which makes a cardinal symptom \*\*\*\*\* which a myocardium falls and produces in the transient \*\*\*\* state, it may die depending on the case and it may result, it is important to carry out the remission of the symptom immediately at the time of the seizure caused by the imbalance of the initial complement of oxygen and the amount of supply. As a chemical used for the treatment of angina, the organic nitro compound, the adrenergic beta receptor antagonist, the calcium channel blocker, etc. are known. [THE pharmacology cull basis OBU therapeutics (The Pharmacological Basis of Therapeutics), the 7th edition, 806 pages, Macmillan (Macmilan), and 1985]. Moreover, substance P, atrial natriuresis hormone, etc. are discovered as matter in the living body to which a crown vessel is made to extend and a crown blood stream is made to increase, and it is [life science (Life Science). Although many matter to which crown vessels, such as the 42nd volume, 695 pages, 1987], and dipyridamole, are made to extend is also compounded, the seizure of angina has few effects and it is chiefly used for the purpose of relapse prevention of an anginal attack [THE pharmacology cull basis OBU therapeutics (The Pharmacological Basis of Therapeutics), the 7th edition, 806 pages, KUMIRAN (Macmilan), and 1985].

[0003] Although pressure of business of an organic nitro compound, especially the nitroglycerin is conventionally carried out most in clinical for the purpose of the remission of an anginal attack, it is easy to receive the first time passage effect in nitroglycerin, there is a fault with the extremely short operation persistence time, and, moreover, headache, a vertigo, the tachycardia accompanying blood pressure descent, etc. are known as a side effect. Then, it looked forward to the angina therapeutic drug which does not have these faults and moreover does not have a side effect.

[0004] On the other hand, let the fall of the S wave in a patient's electrocardiogram, and a T wave be one index in a diagnosis and treatment of angina in clinical. A therapeutic drug effective in anginal attacks, such as nitroglycerin [Japanese journal OBU pharmacology by which this method is often used for reference of an angina therapeutic drug since the fall of the S wave induced by the animal with the medicine is suppressed (The Japanese Journal of Pharmacology), The 20th volume, the 313rd page, 1970, application pharmacology, the 19th volume, the 311st page, 1980, the Japanese journal OBU pharmacology (The Japanese Journal of Pharmacology), the 63rd volume, the 35th page, 1993 and a Japanese pharmacology magazine, the 102nd volume, the 85th page, and 1993 --].

[0005] The matter which suppresses the fall of the S wave induced by the animal with the medicine is variously reported besides nitroglycerin as a result of such reference. For example, although the extract [the Japanese journal OBU pharmacology (The Japanese Journal of Pharmacology), the 20th volume, 313 pages, and 1970] of the whale heart etc. is known Many of those matter Dichloroisoproterenol [journal OBU pharmacology - and - experimental therapeutics () [ The Japanese Journal of Pharmacology and Experimental ] Therapeutics, the 136th volume, 327 pages, 1962], The verapamil (application pharmacology, the 19th volume, 311 pages, 1980), KRN2391 [the

Japanese journal OBU pharmacology (The Japanese Journal of Pharmacology), the 63rd volume, 35 pages, and 1993], PARONIJIPIN (a Japanese pharmacology magazine, the 102nd volume, the 85th page, 1993) etc. is the compounded organic compound. The side effect had become a problem. Moreover, although it is known that the nitro compound of an amino acid derivative will also increase a crown blood stream (JP,2-169558,A and JP,5-221949,A), it is not shown clearly to the fall of the S wave induced by the animal with the medicine whether it is effective.

[0006] On the other hand, much invention is indicated about the peptide which has an antibacterial action to various microorganisms. For example, phosphono tripeptide effective in a gram positive and a gram negative (JP,57-106689,A), A phosphono dipeptide derivative (JP,58-13594,A), a cyclic-peptide derivative (JP,58-213744,A), The peptide which shows antibacterial and an antiviral action (JP,59-51247,A), a glycopeptide derivative (JP,60-172998,A --) effective in a polypeptide (JP,60-130599,A) effective in yeast, and a gram positive JP,61-251699,A and JP,63-44598,A, An oligopeptide effective in a gram positive (JP,62-22798,A), a peptide antibiotic (JP,62-51697,A and JP,63-17897,A) -- the antibacterial peptide (JP,2-53799,A) extracted from the corpuscle of the king crab from North America in addition to this -- There are antibacterial PEPUCHIDODO (\*\*\*\*\* No. 500084 [ two to ] official report) isolated from the hemolymph of a honeybee, an antibacterial peptide (JP,2-268198,A) isolated from royal jelly.

[0007] Lactoferrin is iron unity protein which exists in the body fluid of mammalian including Homo sapiens, such as milk and saliva, a tear, and mucosa secretion liquid, and it is known that an antibacterial action is shown to detrimental microorganisms, such as Escherichia coli, the Candida bacillus, and the Clostridium bacillus, [journal OBU PEDIATORIKUSU (Journal of Pediatrics), the 94th volume, the 1st page, and 1979]. Moreover, having an antibacterial action by the concentration of 0.5-30mg/ml is known to staphylococcus and the enterococcus [a journal OBU daily science (Journal of Dairy Science), the 67th volume, the 606th page, and 1984].

[0008] The artificers of this invention did not have the side effect (for example, antigenicity) which is not desirable paying attention to antibacterial [ of lactoferrin ], moreover, from non-decomposed lactoferrin, found out having antibacterial [ strong thermal resistance and antibacterial / strong ], and already performed patent application (JP,5-320068,A).

[0009] Moreover, the artificers of this invention are antibacterial peptides (JP,5-92994,A) which compound the peptide or peptide derivative which has isolation or the same amino acid sequence as those peptides for the peptide which has strong antimicrobial activity from the decomposition product of lactoferrin, and consist of 20 amino acid residues. Patent application of the antibacterial peptide (JP,5-78392,A) which consists of 11 amino acid residues, the antibacterial peptide (JP,5-148297,A) which consists of six amino acid residues, the antibacterial peptide (JP,5-1498296,A) which consists of five amino acid residues, and the antibacterial peptide (JP,5-148295,A) which consists of 3-6 amino acid residues was already carried out, respectively.

[0010] Furthermore, in the bioactive peptide of milk, it is a calcium absorption promotion peptide (hood chemical \*\* the 11th volume, the 33rd page, 1988) besides a growth hormone, a cell differentiation growth factor, etc. Opioid-peptide [HOPPE-ZAIRAZU Die Zeit SHURIFUTO FUYUA FIJIOROGISSHIE HEMI (Hoppe-Seyler's Zeitschrift fur Physiologische Chemie), the 360th volume, the 1211st page, 1979 and THE Journal of Biological Chemistry (The Journal of Biological Chemistry), The 254th volume, the 2446th page, 1979], the angiotensin converting enzyme inhibitor peptide (hood chemical \*\* the 11th volume, the 39th page, 1988), the peptide (JP,5-262793,A) that has gastric-acid secretion depressant action are known. It found out that there was a cerebral protective action to the derivative of the peptide which has the same amino acid sequence as the matter which hydrolyzed lactoferrin with the acid or the enzyme, or these peptides, and the artificers of this invention also already did patent application to it (Japanese Patent Application No. No. 327738 [ four to ]). However, it is not known that an angina curative effect is in the peptide of these lactoferrin origins, and it is not indicated by reference, either.

[0011]

[Problem(s) to be Solved by the Invention] It has a continuous remission operation to an anginal attack, and, moreover, the medicine with them is not realized so that clearly from the aforementioned conventional technology. [ there are few side effects and safe ] This invention is made in view of the situation as above, and there are few side effects and it aims to let them offer a little and effective

angina therapeutic drug.

[0012]

[Means for Solving the Problem] This invention provides either of the array number 1 to the array numbers 31 with the anginal drug which makes an active principle the derivative of the peptide which has the amino acid sequence of a publication, and these peptides permitted pharmacologically, the salts (these may be hereafter indicated to be peptides collectively) of these peptides permitted pharmacologically, or two or more sorts of such mixture as what solves the aforementioned technical problem.

[0013] That is, with the search method which makes an index depressor effect to the fall of the S wave of the electrocardiogram induced by medication of a medicine, as a result of searching a safe angina therapeutic drug with few side effects, the artificers of this invention found out having the curative effect in which the aforementioned peptides were excellent to angina, and completed this invention. Hereafter, the composition and the desirable mode of this invention are explained in detail.

[0014] When manufacturing from lactoferrin the peptides which are the active principle of the anginal drug of this invention, the lactoferrin used as a starting material commercial lactoferrin and the mammals (for example, Homo sapiens, a cow, a sheep, and a goat --) The skim milk which is the processing object of these milk, such as a colostrum of a horse, shift milk, nature milk, and a late lactation milk The lactoferrin separated from the whey etc. by the conventional method (for example, ion exchange chromatography), It is the metal saturation or partial saturation lactoferrin which carried out the chelate of the appointment lactoferrin which carried out the deferrization of them by the hydrochloric acid, the citric acid, etc., and the appointment lactoferrin with metals, such as iron, copper, zinc, and manganese, and the preparation manufactured by commercial elegance or the well-known method can also be used.

[0015] The peptides used in this invention are the salts permitted pharmacologically or such arbitrary mixture of the derivatives of the peptides which have the peptide obtained from the decomposition product of lactoferrin by the separation means, the same amino acid sequence as this peptide, and a homology amino acid sequence, and these peptides, and these peptides, and it can also be chemically compounded by the well-known method. These peptides can be obtained by the method indicated by each invention of for example, aforementioned JP,5-92994,A, JP,5-78392,A, JP,5-148297,A, JP,5-1498296,A, and JP,5-148295,A.

[0016] The peptide obtained by the aforementioned method can illustrate the peptide which has the following amino acid sequence, its derivative, or salts as a desirable mode. For example, the peptide which has the amino acid sequence of the array numbers 1, 2, and 27, The salts or its derivative (JP,5-78392,A), the peptide that has the amino acid sequence of the array numbers 3, 4, 5, and 6, The salts or its derivative (JP,5-148297,A), the peptide that has the amino acid sequence of the array numbers 7, 8, 9, and 31, The peptide which has the salts or its derivative (JP,5-1498296,A), the array number 10, or the amino acid sequence of 21, They are the salts or its derivative (JP,5-148295,A), the peptide that has the amino acid sequence of 26, 28, 29, and 30 from the array number 22, its salts, or its derivative (JP,5-92994,A). As salts of the aforementioned peptide permitted pharmacologically, acid addition salts, such as a hydrochloride, phosphate, a sulfate, a citrate, a lactate, and a tartrate, can be illustrated, and the derivative which amidated or acylated the carboxyl group can be illustrated as a derivative.

[0017] The medical treatment agent of this invention can be processed into a tablet, a capsule, a troche agent, a syrup agent, a granule, powder, an injection agent, etc. by the well-known method, and can also be used as the medicine which gave the twist agent hide to the well-known method if needed, for example, an enteric tablet. Although the anginal drug of this invention changes with age, symptoms, etc., even if there are per weight of 1kg, it can be prescribed for the patient in taking orally at a rate of 10mg parenterally [ even if few per weight of 1kg / come out / 10microg / comparatively and ]. [ few ]

[0018] Next, the example of an examination is shown and this invention is explained in detail. the example 1 of an examination -- this examination went to the well which investigates the angina curative effect of a peptide

1) It was used at random, having divided the with an examination animal weights [ 220-280g ]

Wistar (Wistar) system male rat (from a Japanese SLC company to purchase) into four groups (one groups [ 6-13 ]).

2) The test-method rat was anesthetized by urethane (Tokyo Chemicals company make) 1.3 mg/kg.i.p., the potential of the heart guided the 2nd time through the electrode with which the limbs were equipped was amplified with the multi-purpose recorder (Nihon Kohden Corp. make), and frequency analysis equipment (Ono Sokki Co., Ltd. make) detected the minimum value of an electrocardiogram. This was made into the value of an S wave and recorded with time with the personal computer (NEC Corp. make). The fall of an S wave \*\*\*\*\*ed and induced BASOPURESHIN(made in peptide lab) 0.5microg/kg through the cannula inserted into the femoral vein, and made the difference of the value in front of \*\*\*\*-ed medication, and the minimum value for 5 minutes after BASOPURESHIN medication the amount of value changes of an S wave. [0019] It dissolved in a physiological salt solution for injection (Otsuka Pharmaceutical make), and \*\*\*\*-ed (peptide of the array number 26 manufactured by the same method as the example 1 of reference) was prescribed for the patient at a rate of 0.5 ml/rat. Nitroglycerin (Nippon Kayaku Co., Ltd. make) was used without diluting an injection agent. Any medicine was prescribed for the patient into the femoral vein through cannula at BASOPURESHIN medication 2 quota, and the control group was medicated with a physiological salt solution. The amount of value changes of an S wave authorized the statistical significant difference by U official approval of Mann-Whitney.

3) an examination result -- the result of this examination is as being shown in Table 1 \*\*\*\*-ed suppressed the fall of the S wave induced by jet injection of the vasopressin, and having been more effective than the nitroglycerin of an active placebo was admitted so that clearly from Table 1. In addition, although examined about other peptides, the almost same result was obtained.

[0020]

[Table 1]

投 与 薬 物	用 量	例数	S波値の変化量 (μV)
生 理 食 塩 液		13	-135±18
ニトログリセリン	1	9	-64±12*
配列番号260ペプチド	0.5	8	-67±30*
	1	6	-33±13**

(注)

1) 用量の単位は、mg/kg

2) S波値の変化量の表示は、平均値±標準誤差

3) \*及び\*\*は、マンローホイットニーのU検定により生理食塩液投

与群と比較し、それぞれ5%未満及び1%未満の危険率で有意差

のあることを示す

[0021] the example 2 of an examination -- this examination went to the well which investigates the angina curative effect of a peptide

1) It was used at random, having divided the with an examination animal weights [ 220-280g ] Wistar (Wistar) system male rat (from a Japanese SLC company to purchase) into four groups (one groups [ 6-9 ]).

2) At a rate of 0.1 ml/min, carry out continuous intravenous drip infusion of the fall of a test-method S wave, and it induces isoproterenol (Nikken Chemicals make) 5microg/kg/min. The difference with the value in every minute was made into the amount of value changes of an S wave after the value in

front of test drug (peptide of array number 26 manufactured by same method as example 1 of reference) medication, and \*\*\*\*-ed medication, And the medicine was examined by the same method as the example 1 of an examination except for having medicated isoproterenol medication start 1 quota.

3) an examination result -- the result of this examination is as being shown in Table 2 \*\*\*\*-ed suppressed notably the fall of the S wave induced by isopropanal tenor's continuous intravenous drip infusion so that clearly from Table 2. In addition, although examined about other peptides, the almost same result was obtained.

[0022]

[Table 2]

投 与 薬 物	用 量	例数	薬物投与後時間 (分) と S 波値の変化量 ( $\mu V$ )					
			1	2	3	4	5	6
生 理 食 塩 液		9	-32 $\pm$ 7	-45 $\pm$ 24	-39 $\pm$ 15	-110 $\pm$ 18	-131 $\pm$ 13	-127 $\pm$ 18
ニトログリセリン	1	6	9 $\pm$ 7***	-3 $\pm$ 18	-38 $\pm$ 32	-56 $\pm$ 36	-106 $\pm$ 35	-98 $\pm$ 43
250mgのペプチド	0.2	6	-6 $\pm$ 7*	-10 $\pm$ 16	-50 $\pm$ 18	-57 $\pm$ 11	-113 $\pm$ 15	-114 $\pm$ 16
	0.5	7	-4 $\pm$ 5**	-19 $\pm$ 18	-32 $\pm$ 19	-18 $\pm$ 14**	-39 $\pm$ 18**	-70 $\pm$ 21

(注)

1) 表1の注と同じ。ただし、\*\*\*はマン-ホイットニーのU検定により生理食塩液投与群と比較し、0.1%未満の危険

率で有意差のあることを示す

[0023] the example 3 of an examination -- this examination went to the well which investigates the angina curative effect of a peptide

1) It was used at random, having divided the with an examination animal weights [ 220-280g ] Wistar (Wistar) system male rat (from a Japanese SLC company to purchase) into six groups (one groups [ 5-9 ]).

2) The fall of a test-method S wave was examined by the same method as the example 2 of an examination except for having carried out continuous intravenous drip infusion of dopamine (Nippon Shinyaku Co., Ltd. make) 0.5mg/kg/min, and having induced it at a rate of 0.1 ml/min.

3) an examination result -- the result of this examination is as being shown in Table 3 \*\*\*\*-ed (peptide of the array number 26 manufactured by the same method as the example 1 of reference) suppressed the fall of the S wave induced by the continuous intravenous drip infusion of a dopamine, and having been more effective than the nitroglycerin of standard medicine was admitted so that clearly from Table 3. In addition, although examined about other peptides, the almost same result was obtained.

[0024]

[Table 3]

投与薬物	用量	例数	薬物投与後時間 (分) とS波値の変化量 ( $\mu V$ )					
			1	2	3	4	5	6
生理食塩液		9	-37 $\pm$ 4	-18 $\pm$ 5	-151 $\pm$ 23	-133 $\pm$ 23	-198 $\pm$ 23	-191 $\pm$ 22
ニトログリセリン	1	8	7 $\pm$ 8***	5 $\pm$ 6**	-56 $\pm$ 14**	-89 $\pm$ 21*	-101 $\pm$ 18*	-100 $\pm$ 18*
E757号250ペプチド	0.05	6	-39 $\pm$ 10	-33 $\pm$ 12	-142 $\pm$ 28	-162 $\pm$ 37	-173 $\pm$ 39	-181 $\pm$ 36
	0.1	6	-23 $\pm$ 9	-11 $\pm$ 11	-136 $\pm$ 22	-165 $\pm$ 37	-181 $\pm$ 35	-187 $\pm$ 37
	0.2	5	-8 $\pm$ 12*	31 $\pm$ 12***	-62 $\pm$ 31*	-117 $\pm$ 46	-126 $\pm$ 51	-132 $\pm$ 48
	0.5	6	-2 $\pm$ 6**	29 $\pm$ 11***	-9 $\pm$ 13***	-40 $\pm$ 18**	-52 $\pm$ 20**	-65 $\pm$ 19**

(注)

1) 表2の注と同じ。

[0025] the example 4 of an examination -- this examination went to the well which investigates the acute toxicity of a peptide

1) It was used at random using the both sexes of the rat (from Japan SLC to purchase) of CD (SD) system of 6 weeks old of use animals, respectively, having divided the male and the female into four groups (one groups [ five ]).

2) per [ 1000 and 2000 ] test-method weight of 1kg, and the 4000mg peptide which came out of comparatively and which was manufactured by the same method as the example 1 of reference-- injection -- service water (Otsuka Pharmaceutical make) -- dissolving -- 4ml per weight of 100g -- it came out comparatively, single time forcible internal use was carried out using the needle with a metal ball, and acute toxicity was examined

3) an examination result -- the result of this examination is as being shown in Table 4 The example of death was not accepted in the group which prescribed this peptide for the patient at a rate of 1000mg [ kg ] /and 2000mg/kg so that clearly from Table 4. Therefore, LD50 of this peptide is 2000mg/kg or more, and the very low thing made toxicity clear. In addition, although examined about other peptides, the almost same result was obtained.

[0026]

[Table 4]

用量 (mg/kg)	死亡数/例数	
	雄	雌
0	0/5	0/5
1000	0/5	0/5
2000	0/5	0/5
4000	5/5	5/5

[0027] Cow lactoferrin (sigma company make) 50mg of example of reference 1 marketing was dissolved in 0.9ml of purified waters, pH was adjusted to 2.5 with the hydrochloric acid of 0.1 conventions, pig pepsin (sigma company make) 1mg of back marketing was added, and it hydrolyzed at 37 degrees C for 6 hours. Subsequently, adjusted pH to 7.0 by the sodium hydroxide of a decinormal, and heated for 10 minutes at 80 degrees C, the enzyme was made to deactivate, it cooled



to the room temperature, at-long-intervals heart separation was carried out by 15,000rpm for 30 minutes, and the transparent supernatant liquid was obtained. The vacuum drying of the fraction which applies 100micro of this supernatant liquid l to the high performance chromatography using TSK gel ODS-120T (TOSOH CORP. make), is eluted in 20% acetonitrile which contains TFA (trifluoroacetic acid) 0.05% for 10 minutes after sample pouring by the 0.8ml rate of flow for /, is eluted in the gradient of 20 - 60% of acetonitrile which contains TFA 0.05% for 30 minutes the back, and is eluted in 24 - 25 minutes was collected and carried out. The fractions which dissolve this dry matter in a purified water by 2% (W/V) of concentration, are missing from the high performance chromatography using TSK gel ODS-120T (TOSOH CORP. make) again, are eluted in 24% acetonitrile which contains TFA 0.05% for 10 minutes after sample pouring by the 0.8ml rate of flow for /, are eluted in the gradient of 24 - 32% of acetonitrile which contains TFA 0.05% for 30 minutes the back, and are eluted in 33.5 - 35.5 minutes were collected. The above-mentioned operation was repeated 25 times, and carried out the vacuum drying, and peptide about 1.5mg was obtained.

[0028] The above-mentioned peptide was understood an added water part with 6-N hydrochloric acid, and the amino acid composition was analyzed by the conventional method using the amino acid analyzer. 25 times of Edman degradation was performed for the same sample using gaseous-phase seeking ENSA - (applied biotechnology systems company make), and the array of 25 amino acid residues was determined. Moreover, it checked that a disulfide bond existed by the disulfide-bond analysis method [Analytical Biochemistry (Analytical Biochemistry), the 67th volume, the 493rd page, and 1975] using DTNB [a 5 and 5-dithio-screw (2-nitrolycerine benzoic acid)].

[0029] Consequently, having the amino acid sequence of the array number 26 which this peptide consisted of 25 amino acid residues, the 3rd and the 20th cysteine residue carried out the disulfide bond, two amino acid residues combined with the N terminus side from the 3rd cysteine residue, and five amino acid combined with C-end side from the 20th cysteine residue, respectively was checked. Example of reference 2 peptide automatic synthesizer unit (Pharmacia LKB Biotechnology, Inc. make.) Based on the solid phase peptide synthesis method [journal OBU chemical society Perkin I (Journal of Chemical Society Perkin I), the 538th page, and 1981] by German shepherd etc., the peptide was compounded as follows using LKBBiolynx4170.

[0030] Amino acid [less-or-equal Fmoc-amino acid or Fmoc which protected the amine functional group by 9-fluorenyl methoxycarbonyl group - Added N and N-dicyclohexylcarbodiimide to] which may be indicated to be the name (for example, Fmoc-asparagine) of peculiar amino acid, it was made to generate the anhydride of desired amino acid, and this Fmoc-amino acid anhydride was used for composition. In order to manufacture a peptide chain, the Fmoc-asparagine anhydride equivalent to the asparagine residue of C-end is fixed to a URUTOROSHIN A resin (Pharmacia LKB Biotechnology, Inc. make) by making a dimethylamino pyridine into a catalyst through the carboxyl group. Subsequently, this resin is washed by the dimethylformamide containing a piperidine, and the protective group of the amine functional group of C-end amino acid is removed. Distributor shaft coupling of the Fmoc-arginine anhydride which is equivalent to the 2nd from C-end of an after amino acid sequence was carried out to the deprotection amine functional group of the arginine fixed to the resin through the aforementioned C-end amino acid residue. The glutamine, the tryptophan, the glutamine, and the phenylalanine were fixed one by one like the following. After distributor shaft coupling of all amino acid was completed and the peptide chain of a desired amino acid sequence was formed, TFA, 5% phenol, and the solvent that consists of an ethanediol 1% performed removal of protective groups other than an acetamide methyl, and desorption of a peptide 94%, the high performance chromatography refined the peptide, this solution was condensed, it dried and peptide powder was obtained.

[0031] The amino acid composition was analyzed by the conventional method using the amino acid analyzer about the aforementioned peptide, and it checked having the amino acid sequence of the array number 10.

[0032]

[Example] Next, although an example is shown and this invention is explained still in detail and concretely, this invention is not limited to the following examples.

an example -- 1mg of peptide powder of the array number 26 manufactured by the same method as the example 1 of reference to 1ml (Otsuka Pharmaceutical make) of service water 1 \*\*\*\*, and 9mg

of sodium chlorides (product made from the Wako Pure Chem industry) -- it came out comparatively, and dissolved, filtration sterilization of the pH was adjusted and carried out to about 7 with the sodium hydroxide (Wako Pure Chem industrial company make) and the hydrochloric acid (Wako Pure Chem industrial company make), it filled up ampul with 1ml at a time by the conventional method, and the example 2 injection -- the method same to 1ml (Otsuka Pharmaceutical make) of service water as the example 2 of reference It dissolved at a 10mg [ of peptide powder of the manufactured array number 10 ], and D-mannite (Wako Pure Chem industrial company make) 49.5mg rate, filtration sterilization of the pH was adjusted and carried out to about 7 in the solution of phosphoric-acid buffer powder (Wako Pure Chem industrial company make), and it filled up the vial bottle with 1ml at a time by the conventional method, and it freeze-dried and the angina therapeutic drug for injection was manufactured.

The angina therapeutic drug of the tablet which consists of the following composition per example 31 lock was manufactured by the following method.

[0033]

Peptide of the dividend number 26 10.0 (mg)

Lactose monohydrate (Wako Pure Chem industrial company make) 30.0 Corn starch (Wako Pure Chem industrial company make) 19.8 Crystalline cellulose (Asahi Chemical Industry Co., Ltd. make) 28.0 Magnesium-silicate 5 hydrate (Wako Pure Chem industrial company make) 2.0 Magnesium stearate (Wako Pure Chem industrial company make) The same method as the example 1 of 0.2 reference. It kneads into the mixture of the peptide of the manufactured array number 26, a lactose monohydrate, corn starch, and a crystalline cellulose uniformly, adding a sterilized pure water suitably, and it was dried at 50 degrees C for 3 hours, and magnesium-silicate 5 hydrate and the magnesium stearate were added to the obtained dry matter, and it mixed to it, and tableted with the tableting vessel by the conventional method.

[0034]

[Effect of the Invention] The effect of this invention relating to the anginal drug which makes peptides an active principle, and being done so by this invention is as follows as explained in detail above. (1) There are few toxicity and side effects.

(2) There is thermal resistance; and in water, it is fusibility and is stable as eye a stable hatchet and a medicine in solution.

(3) Since a peptide has an antibacterial action, it does not need to use antiseptics in tablet-izing.

[0035]

[Layout Table]

array number: -- length [ of one array ]: -- mold [ of 11 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and the peptide which contains this peptide as fragmentation It sets in the following array and is R01. Cys The arbitrary amino acid residues to remove are shown.

[0036]

array: -- Lys R01 R01 R01 R01 R01 Gln R01 R01 Met Lys Lys1 5 10 array number: -- length [ of two arrays ]: -- mold [ of 11 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation It sets in the following array and is R01. Cys The arbitrary amino acid residues to remove are shown.

[0037]

array: -- Lys R01 R01 R01 R01 Gln R01 R01 Met Arg Lys1 5 10 array number: -- length [ of three arrays ]: -- mold [ of six arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation It sets in the following array and is R01. Cys The arbitrary amino acid residues to remove are shown.

[0038]

array: -- Arg R01 R01 R01 R01 Arg1 5 array number: -- length [ of four arrays ]: -- mold [ of six arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation It sets in the

following array and is R01. Cys The arbitrary amino acid residues to remove are shown.

[0039]

array: -- Lys R01 R01 R01 R01 Arg1 5 array number: -- length [ of five arrays ]: -- mold [ of six arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation It sets in the following array and is R01. Cys The arbitrary amino acid residues to remove are shown.

[0040]

array: -- Lys R01 R01 R01 R01 Lys1 5 array number: -- length [ of six arrays ]: -- mold [ of six arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation It sets in the following array and is R01. Cys The arbitrary amino acid residues to remove are shown.

[0041]

array: -- Arg R01 R01 R01 R01 Lys1 5 array number: -- length [ of seven arrays ]: -- mold [ of five arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation It sets in the following array and is R01. Cys The arbitrary amino acid residues to remove are shown.

[0042]

array: -- Arg R01 R01 R01 Arg1 5 array number: -- length [ of eight arrays ]: -- mold [ of five arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation It sets in the following array and is R01. Cys The arbitrary amino acid residues to remove are shown.

[0043]

array: -- Lys R01 R01 R01 Arg1 5 array number: -- length [ of nine arrays ]: -- mold [ of five arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation It sets in the following array and is R01. Cys The arbitrary amino acid residues to remove are shown.

[0044]

array: -- Arg R01 R01 R01 Lys1 5 array number: -- length [ of ten arrays ]: -- mold [ of six arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation

[0045]

array [ :P ] he Gln Trp Gln Arg Asn1 5 array number: -- length [ of 11 arrays ]: -- mold [ of five arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation

[0046]

array [ :P ] he Gln Trp Gln Arg1 5 array number: -- length [ of 12 arrays ]: -- mold [ of four arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation

[0047]

array: -- Gln Trp Gln Arg1 array number: -- length [ of 13 arrays ]: -- mold [ of three arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and the peptide which contains this peptide as fragmentation

[0048]

array: -- Trp Gln Arg1 array number: -- length [ of 14 arrays ]: -- mold [ of five arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and the peptide which contains this peptide as fragmentation

[0049]

array: -- Arg Arg Trp Gln Trp1 5 array number: -- length [ of 15 arrays ]: -- mold [ of four arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation

[0050]

array: -- Arg Arg Trp Gln1 array number: -- length [ of 16 arrays ]: -- mold [ of four arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and the peptide which contains this peptide as fragmentation

[0051]

array: -- Trp Gln Trp Arg1 array number: -- length [ of 17 arrays ]: -- mold [ of three arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and the peptide which contains this peptide as fragmentation

[0052]

array: -- Gln Trp Arg1 array number: -- length [ of 18 arrays ]: -- mold [ of six arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and the peptide which contains this peptide as fragmentation

[0053]

array: -- Leu Arg Trp Gln Asn Asp1 5 array number: -- length [ of 19 arrays ]: -- mold [ of five arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation

[0054]

array: -- Leu Arg Trp Gln Asn1 5 array number: -- length [ of 20 arrays ]: -- mold [ of four arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and peptide which contains this peptide as fragmentation

[0055]

array: -- Leu Arg Trp Gln1 array number: -- length [ of 21 arrays ]: -- mold [ of three arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and the peptide which contains this peptide as fragmentation

[0056]

array: -- Arg Trp Gln1 array number: -- length [ of 22 arrays ]: -- mold [ of 20 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and the peptide which contains this peptide as fragmentation It sets in the following array and they are No. 2. Cys and No. 19 Cys is carrying out the disulfide bond.

[0057]

Array: Lys Cys Arg Arg Trp Gln Trp Arg Met Lys Lys Leu Gly Ala Pro 1 5 10 15 Ser Ile Thr Cys Val 20 array number: -- length [ of 23 arrays ]: -- mold [ of 20 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- let this peptide and this peptide be fragmentation The included peptide. In order that Cys\* may prevent formation of a disulfide bond in the following array, the cysteine which embellished the thiol group chemically is shown.

[0058]

Array: Lys Cys\* Arg Arg Trp Gln Trp Arg Met Lys Lys Leu Gly Ala Pro 1 5 10 15 Ser Ile Thr Cys\* Val 20 array number: -- length [ of 24 arrays ]: -- mold [ of 20 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- let this peptide and this peptide be fragmentation The included peptide. It sets in the following array and they are No. 2. Cys and No. 19 Cys is carrying out the disulfide bond.

[0059]

Array: Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Lys Val Arg Gly Pro 1 5 10 15 Pro Val Ser Cys Ile 20 array number: -- length [ of 25 arrays ]: -- mold [ of 20 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- let this peptide and this peptide be fragmentation The included peptide. In order that Cys\* may prevent formation of a disulfide bond in the following array, the cysteine which embellished the thiol group chemically is shown.

[0060]

Array: Lys Cys\* Phe Gln Trp Gln Arg Asn Met Arg Lys Val Arg Gly Pro 1 5 10 15 Pro Val Ser Cys\* Ile 20 array number: -- length [ of 26 arrays ]: -- mold [ of 25 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- let this peptide and this peptide be fragmentation The included peptide. It sets in the following array and they are No. 3. Cys and No. 20 Cys is carrying out the disulfide bond.

[0061]

Array: Phe Lys Cys Arg Arg Trp Gln Trp Arg Met Lys Lys Leu Gly Ala 1 5 10 15 Pro Ser Ile Thr Cys Val Arg Arg Ala Phe 20 25 array number: -- length [ of 27 arrays ]: -- mold [ of 11 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- let this peptide and this peptide be fragmentation The included peptide.

[0062]

配列:

Lys Thr Arg Arg Trp Gln Trp Arg Met Lys Lys

1

5

10

array number: -- length [ of 28 arrays ]: -- mold [ of 38 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- this peptide and the peptide which contains this peptide as fragmentation It sets in the following array and they are No. 16. Cys and No. 33 Cys is carrying out the disulfide bond.

[0063]

Array: Lys Asn Val Arg Trp Cys Thr Ile Ser Gln Pro Glu Trp Phe Lys 1 5 10 15 Cys Arg Arg Trp Gln Trp Arg Met Lys Lys Leu Gly Ala Pro Ser 20 25 30 Ile Thr Cys Val Arg Arg Ala Phe 35 array number: -- length [ of 29 arrays ]: -- mold [ of 32 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- let this peptide and this peptide be fragmentation The included peptide. It sets in the following array and they are No. 10. Cys and No. 27 Cys is carrying out the disulfide bond.

[0064]

Array: Thr Ile Ser Gln Pro Glu Trp Phe Lys Cys Arg Arg Trp Gln Trp 1 5 10 15 Arg Met Lys Lys Leu Gly Ala Pro Ser Ile Thr Cys Val Arg Arg 20 25 30 Ala Phe array number: -- length [ of 30 arrays ]: -- mold [ of 47 arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- let this peptide and this peptide be fragmentation The included peptide. In the following array, it is the length 36 of an array, and they are No. 9, No. 26, and No. 35. No. 9 of the peptide which has Cys Cys and No. 26 Cys carries out a disulfide bond and they are No. 35 of the peptide of the length 36 of the above-mentioned array. No. 10 of the peptide to which Cys is the length 11 of an array and has Cys in No. 10 Cys is carrying out the disulfide bond.

[0065]

Array: Val Ser Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn 1 5 10 15 Met Arg Lys Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp 20 25 30 Ser Pro Ile Gln Cys Ile 35 Gly Arg Arg Arg Arg Ser Val Gln Trp Cys Ala 1 5 10 array number: -- length [ of 31 arrays ]: -- mold [ of five arrays ]: -- amino acid topology: -- kind [ of straight chain-like array ]: -- feature [ of a peptide array ]: -- let this peptide and this peptide be fragmentation The included peptide. It sets in the following array and is R01. The arbitrary amino acid residues except Cys are shown.

[0066]

Array: Lys R01 R01 R01 Lys 1 5.

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[Translation done.]